CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
METHOMYL

Chemical Code # 000383, Tolerance # 00253
SB 950 # 169

August 8, 1986
Revised 11/6/87, 6/15/88, 7/21/89, 1/10/90, 9/15/97, 5/2/98, and 1/12/99

I. DATA GAP STATUS

Chronic, rat:	No data gap, possible adverse effect
Chronic, dog:	No data gap, possible adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect (not oncogenicity)
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosomal aberration:	No data gap, no adverse effect
DNA damage/repair:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time*

* An acute neurotoxicity study in the rat identified a possible adverse effect (tremors). A subchronic rat neurotoxicity study did not indicate adverse effects. Both of these studies were acceptable. One unacceptable hen neurotoxicity study is on file.

Note, Toxicology one-liners are attached
** indicates acceptable study
Bold face indicates possible adverse effect

II. TOXICOLOGY ONE-LINERS AND DISCUSSION

COMBINED RAT

****253-164, 253-165 037842, 037843** (with rebuttal and supplemental data in -176, 052178): Kaplan, A. M., "Long-Term Feeding Study in Rats with S-Methyl N-[(Methylcarbamoyl)Oxy] Thioacetimidate, (Methomyl; INX-1179), Final Report". (Haskell Laboratory, E. I. du Pont de Nemours and Company, Inc., Wilmington, Delaware, # 235-81, 5/1/81). Methomyl technical 99+%, Lot # INX-1179-255; fed in the diet to 80/sex/group at 0, 50, 100 and 400 ppm (of these, 70/sex/group were designated for the 2 year study, and 10/sex/group were used for a 1-yr interim sacrifice). NOEL = 100 ppm (body weight decrements in both sexes: possible mild anemia). At 400 ppm there were some reductions in RBC parameters (RBC count, Hb concentration, HCT) in high dose females. There was some bone marrow hyperplasia at this dose in males, and slightly elevated extramedullary hematopoiesis in liver, spleen, or adrenals; typically marginal in scope and generally observed in only one sex. CDFA/DPR review history: study was first reviewed by J. Gee, 4/18/86, who classified study as unacceptable and upgradeable (needing individual clinical observation data and historical control hematology data). Re-reviewed by J. Carlisle and F. Martz, 10/9/87. Above requested data were provided, but study was still not acceptable for chronic data requirements for lack of eye exams. Study was considered acceptable as an oncogenicity study. With submission of additional data on eye histopathology for the 2-year dog study (CDFA # 072204), the lack of ophthalmology in the rat study was no longer considered as an issue, and the study was upgraded to **acceptable** as a combined study. Gee, 7/21/89. Re-evaluation and consolidation of older reviews into one document by Green and Aldous, Jan. 12, 1999.

EPA one-liner: Oncogenic NOEL => 400 ppm (HDT). Systemic NOEL = 100 ppm. ChE NOEL **>** 400 ppm (HDT) (Ellman method). Minimum.

CHRONIC RAT

-025, 024197 (With rebuttal and full report in -176, 051310): "22-Month Dietary Feeding - Rats, Lannate Methomyl Insecticide, (S-Methyl-N-[(Methyl-carbamoyl)Oxy]Thioacetimidate), Final Report". (Hazleton Laboratories, Inc., Falls Church, VA., # 201-164, 7/26/68). Lannate methomyl insecticide, 90-100% purity; 35/sex/group was fed at 0, 0, 50, 100, 200, & 400 ppm. Decreased growth at 200 and 400 ppm; dosage-related decrease in hemoglobin in females, accompanied by extramedullary hematopoiesis in the 200 and 400 ppm groups. Renal tubular dilation, hypertrophy, vacuolation at 200 and 400 ppm. Overall NOEL = 100 ppm. Unacceptable, but useful supplementary information. Reviewed by J. Gee, 5/22/86. Additional information (Document No. 253-176) led to no change in status. J. Carlisle, 7/16/87. [See acceptable combined study, above].

EPA one-liner: One year report, systemic NOEL = 100 ppm and ChE NOEL = 400 ppm (HDT).

-008, 042606; -025, 024024; -090, 963995; and 407-003, 024988-89 are summaries of 051310.

often with swelling/irregularity of the cells, and pigmentation of spleen in 400 ppm males). Common high dose findings, typically in both sexes, included the above observations, plus hematology changes (reduced HCT, Hb, RBC counts), extramedullary hematopoiesis in spleen, and increased hematopoiesis in marrow. Findings are considered to indicate "possible adverse effects". The findings which defined the LOEL were typically either uncommon findings which were "slight" in degree, or were findings commonly seen in dogs, but somewhat increased in degree over the norm. For this reason, these results do not suggest pivotal findings for toxicity evaluation. One high dose male had sustained hematology changes, plus marked changes consistent with severe anemia (greatly enlarged spleen and liver, and severe extramedullary hematopoiesis in these organs). A summary of the CDFA/DPR evaluations of this study is included in the background section of this review. This review provides tabular data supporting previous conclusions regarding methomyl toxicity. Green and Aldous, 12/22/98.

Data review history of Record No. 037845, above: The 1985 "reviews" by Apostolou and Aldous on this study were simply references to brief summary data in Document/Record Nos. 253-025:024203 and 407-003:033910. These submissions were by Shell and Union Carbide, respectively. The "final report" was later submitted as Document/ Record Nos. 253-167:037845, submitted by du Pont in October, 1985. E. I. du Pont de Nemours and Company has been the primary or exclusive source of data since then, and has retained the Tolerance No. of 253. The 1986 CDFA review by de Vlaming and Gee highlighted study results and identified study deficiencies, including a lack of ophthalmology data. A rebuttal response to Document No. 253-176 (no record number) shows all data requirements except for ophthalmology to be satisfied (J. Carlisle and F. Martz, 11/6/87). A meeting of E. I. du Pont de Nemours and Company representatives and CDFA (including CDFA reviewers J. Carlisle and F. Martz) was held on 6/14/88, in which it was agreed that du Pont should submit histopathology data based on multiple sections of eyes to address the primary remaining deficiency of the dog chronic study. Following submission of the dog eye histopathology data (Document/Record No. 253-186:072204), the study was upgraded to acceptable status (J. Gee, 7/18/89). There were no treatment-related ocular effects. The Dec. 1998 examination of the original report provides data tables which can be used for risk assessment evaluation. Aldous, 12/22/98.

EPA one-liner: Systemic NOEL = 100 ppm. Enlargement of prostate gland. Increase kidney pigmentation and swelling of the proximal convoluted tubules. Minimum.

-008, -025, -090, 024203, 042607, 035859; and 407-003, 033910 are summaries of 037845-46.

-186 072204 Supplement to 037845. Results of additional sections of the eyes made as a result of the meeting held April 21, 1988, between the registrant and CDFA.

ONCOGENICITY MOUSE

**253-166 037844, "104-week Chronic Toxicity and Carcinogenicity Study in Mice", (David G. Serota, Hazleton Laboratories America, Inc, Report # HLO-253-81, Project # 201-510, 12

REPRODUCTION RAT

253-177 051313 Lu, C. C., “Nudrin® two-generation reproduction study in rats”, WIL Research Laboratories, Inc., 12/13/82. Laboratory Study # WRC RIR-275. CD® rats were tested in a 2-generation study with one littering period per generation at dietary levels of 0, 75, 600, or 1200 ppm NUDRIN® (SD-14999 Technical = methomyl). Groups sizes were 13 males and 26 females for F0 parents, and 20 males and 40 females for F1 parents. A conservative NOEL for reproductive and non-reproductive effects is 3.5 mg/kg/day (typical intake of 75 ppm rats which were not rapidly growing, prior to mating). Substantially higher intake on an animal weight basis for 75 ppm rats, such as occurred during maternal lactation and rapid growth of young pups, led to marginally reduced pre-weaning pup body weights and reduction in weights of young post-weanling rats. These findings corresponded to intakes on the order of at least 14 mg/kg/day for maternal rats and 18 mg/kg/day for rapidly growing offspring. Levels of 600 to 1200 ppm reduced food consumption and body weights in both parental rats and pre-weanling pups. The highest dose reduced pup survival during the first few days of life. There was a marginally reduced live litter size for the 600 ppm parental F1 group, which may have been treatment-related. There were marginal reductions in RBC parameters, in females only, at 600 to 1200 ppm (reduced HCT, Hb, and RBC count). There was a general increase in spleen weights in weanling 1200 ppm pups, without associated histopathology. The latter findings are consistent with those of several other studies. The highest dose elicited clinical signs of “increased activity, pilo erection, depressed righting reflex and myoclonic body tics”. These signs were primarily limited to the first three weeks of treatment. Study remains **acceptable with **no adverse effects**. Re-examination by Aldous, Jan. 12, 1999.

CDFA/DPR review history: An abbreviated version of the present report (Document No. 253-113, Record Nos. 035815 and 035816) was evaluated by de Vlaming and Martz on 1/13/86. They determined that the available data appeared to reflect a viable study, but they did not have the information to do an analysis of the findings. These reviewers requested individual data to upgrade the study. The complete report was later submitted (Document No. 253-177, Record No. 051313). This was examined by Martz and Carlisle (11/6/87). They upgraded the study to acceptable status, but provided only a summary paragraph of the findings. The 1998 worksheet provides tabular presentations and re-analyses of the study results.

EPA One-liner: None in Branch library.

253-255 140400 Hurtt, M. E. (author of supplement). "Nudrin, Two-generation Reproduction Study in the Rat" (Supplement No. 1). Information was sent in response to U.S. EPA request for additional data. CDFA had accepted the study as presented in 1987. Most complete report is Document No. 253-177, Record No. 051313. Final Report Date: 12/13/82. Laboratory Study #: 61531. Mean daily mg/kg/day intakes during premating periods for 75, 600, and 1200 ppm groups were 5, 37, and 74 for F0 males; 5, 39, and 76 for F0 females; 7, 56, and 117 for F1 males; and 7, 59, and 128 mg/kg/day for F1 females. Test article stability was proven over the period of the study, and stability was shown at RT for at least 3 weeks. This supplement included summary data for gross observations, and summary and individual data for clinical

-008, 964001, and -168, 37847 are partial duplicates of #51311.

-008, 024201, -025, 042601, and 407-003, 024990 are summaries of # 051311.

TERATOLOGY RAT

**253-176 051312 (Full report: -008, 96500 and -170, 037854 are partial versions) "Oral Teratogenic Study in Rats with Lannate (INX-1179)", (E. I du Pont de Nemours & Co., Haskell Laboratory, # 498-78, 9/5/78). Lannate (methomyl), 99% purity; was fed in the diet to 25 females per group at 0, 50, 100, or 400 ppm on days 6 through 15 of gestation. NOEL: maternal = 100 ppm (body weight and food consumption); developmental $\geq$ 400 ppm (no effects). Original review by J. Gee, 4-18-86: unacceptable with insufficient information for evaluation. Re-reviewed by F. Martz, 9-11-87: additional information (complete report including diet analysis) did not result in change of status because there was no MTD. On April 21, 1988, a meeting was held with the registrant, and the dose selection was discussed with respect to the oral gavage LD50. As a result, the dose selection was considered as justified and the study was upgraded to acceptable status (Gee, 6/15/88). A worksheet was produced by Aldous on 12/29/98, with no change in study status.

EPA one-liner: NOEL (maternal toxicity) = 100 ppm. Minimum.

-008, 964000, and -170, 37854 are partial reports of #51312.

-025, 24200, and 407-003, 33909 are summaries of #51312.

TERATOLOGY RABBIT

253-170 037855, “Embryo-Fetal Toxicity and Teratogenicity Study of Methomyl in the Rabbit”, Elizabeth L. Feussner (Study Director), Argus Research Laboratories, Inc., Horsham, PA., Report # HLO-331-83, 9/18/83). Twenty artificially-inseminated New Zealand White (DLI:NZW) female rabbits per group received methomyl by gavage at 0, 2, 6, and 16 mg/kg/day on gestation days 7 through 19. Maternal NOEL = 6 mg/kg/day (7 high-dose females died: common signs in this group included tremors, hyperactivity, body jerks, excessive salivation, convulsions, and ataxia). Developmental NOEL = 16 mg/kg/day (no adverse effects**). Initially classified as unacceptable (dosing solution analyses required). Dosing solution analysis, reported in Document No. 253-176, prompted an upgrade to **acceptable** status (see rebuttal response of 11/9/87). CDFA reviews were by de Vlaming and Remsen (Gee), 4/18/86; and Carlisle (in 11/9/87 rebuttal). An updated worksheet (with additional tables) was produced by Green and Aldous on 12/09/98. This re-evaluation did not result in any change of study status.

EPA one-liner: NOEL (teratogenicity and fetotoxicity) > 16 mg/kg/day. Maternal NOEL = 2 mg/kg/day. Minimum.

GENE MUTATION

** -169, 037852 "CHO/HGPRT Assay for Gene Mutation". (Haskell Laboratory, 1/13/84) Methomyl ~ 99%; CHO cells were exposed to 0, 10, 20, 40, 50, or 55 mM (-S9 aroclor-induced rat liver fraction) with EMS as positive control, or 0, 100, 150, 200, 250, or 350 mM (+S9 aroclor-induced rat liver fraction) with DMBA as positive control and selected for resistance to 6-TG; **No increased mutation frequency.** Survival decreased at higher concentration. Complete, acceptable. J. Gee, 4/4/86.
EPA one-liner: Negative. Acceptable.

-169, 037848 "Evaluation of Selected Pesticides as Chemical Mutagens In vitro and In vivo Studies." (SRI, May 1977). Lannate 99% purity, lot no. 6602-82; Salmonella typhimurium strains TA1535, TA1537, TA1538, and TA100 tested at 0, 1, 10, 50, 100, 500, or 1000 µg/plate, with/without S9 (not described). **No increased reversion rate.** Unacceptable (lacks adequate positive controls, no justification of 1000 µg/plate as highest concentration no indication of cytotoxicity), no individual plate counts, no TA98, source of S9 not stated). J. Gee, 4/4/86.
EPA one-liner: None in Branch library.

-025, 142 964002 Reference material, insufficient information for review.

-025, 024205 Reference material, no methomyl data.

CHROMOSOMAL ABERRATION

-169, 037851 "In Vivo Bone Marrow Chromosome Study in Rats, H# 15,000, Final Report." (Hazleton (VA), 12/18/84). Methomyl ~ 99% purity; in water @ 0, 2, 6, & 20 mg/kg, 5/sex/group, by single gavage; Sacrificed @ 6, 24, & 48 hr. **No increase in chromosomal aberrations. Complete, acceptable. J. Gee, 4/1/86.
EPA one-liner: Negative. Acceptable.

DNA DAMAGE

-169, 037853 "Assessment of Methomyl (INX-1179-255) in the In Vitro Unscheduled DNA Synthesis Assay in Primary Rat Hepatocytes." (Haskell Laboratory, 8/2/85). Methomyl, 99% purity; primary rat hepatocytes were exposed to 0, 1, 10, 100, 1000, 5000, & 75,000 µM for 18 hr. **No increase in net grain counts, 4 slides/each concentration, 2 trials. Complete, Acceptable. J. Gee, 4/4/86.
EPA one-liner: None in Branch library.

-169, 037850 "Evaluation of Selected Pesticides as Chemical Mutagens In vitro and In vivo Studies." (SRI, May 1977). Methomyl 99% purity, Saccharomyces cerevisiae were tested in

the acceptable study in mammalian cells, which was negative for UDS, would be given more weight than the study in yeast, especially in view of the deficiencies in the report. Because of the negative findings in other acceptable studies in the area of genotoxicity, the biological significance of the result in yeast is questionable. J. Gee, 11/6/87.

NEUROTOXICITY

HEN

253-171 037856 (with rebuttal in 253-176): "Oral LD_{50} and Delayed Paralysis Tests (Hens)." (Haskell Laboratory, 9/25/67). Methomyl technical, no purity given; was administered in acetone/water mixture at 28 mg/kg to 10 hens (cross of Barred Rock and Rhode Island Red varieties) without atropine; TOCP positive control. Evidently 4/10 died. Four additional hens were dosed with atropine pre-treatment at methomyl doses of 60, 90, 120, or 200 mg/kg (all survived). Salivation, lacrimation, and some convulsions, but no paralysis, were observed in the survivors. No microscopic lesions in sciatic nerve (which was evidently the only histopathologic feature assessed). No paralysis or sciatic nerve lesions arose in hens given 60, 90, 120, or 200 mg/kg with atropine. Original review by J. Gee, 4/12/86, Unacceptable, not upgradeable (no repeat dosing, inadequate protocol and data presentation). Rebuttal containing no additional data did not upgrade study; no change in status. J. Carlisle, 7/22/87. One-liner updated by Green and Aldous, 12/8/98.

EPA one-liner: Negative. Minimum.

-008,-025, 042608, 024202, and 407-003, 024987 are summaries of 037856.

Comment: Delayed neurotoxicity testing is not a current data requirement for this class of compounds. F. Martz, 10/20/87.

RAT

**** 253-272 160438** "Methomyl Technical (DPX-X1179-512): Acute Oral Neurotoxicity Study in Rats"; (K. A. Mikles; E.I. du Pont de Nemours and Co., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Project ID: HL-1998-01080; 2/2/98); Fifty two rats/sex/group were dosed orally by gavage with 0, 0.25, 0.50, 0.75 or 2.0 mg/kg of Methomyl technical (purity: 98.6%). Twelve rats/sex/group were included in the neurobehavioral study in which they were examined in the functional observational battery (FOB) and motor activity assessments prior to dosing, 30 minutes after dosing (day 1) and on study days 8 and 15. Six animals/sex/group of this cohort were randomly chosen for histological examination of the nervous system and muscle. Erythrocyte and plasma blood cholinesterase activities were measured in 10 animals/sex/group of the clinical pathology subgroup on the day prior to dosing, at 30 minutes post-dose (Day 1) and one day after treatment (Day 2). At the latter two time points, brain cholinesterase activities were determined as well. No test material-related mortality

for both the males and females in the 0.75 and 2 mg/kg groups ((M) 77 and 58% of control, (F) 60 and 64% of control, respectively) at 30 minutes post-dose. Erythrocyte cholinesterase was significantly inhibited ($p<0.05$) 30 minutes post-dose for the males in the 2.0 mg/kg group (54% of control) and the females in the 0.5, 0.75 and 2.0 mg/kg (75, 62, and 43% of control, respectively). Brain cholinesterase activity was significantly inhibited ($p<0.05$) 30 minutes after dosing for the males and females in the 0.5, 0.75, and 2.0 mg/kg groups ((M) 81, 75, and 53% of control, (F) 80, 70, and 49% of control, respectively). All of the cholinesterase activity parameters for the treated animals were comparable to those of the control animals by 24 hours after dosing. No gross lesions nor treatment-related neuropathology were evident. **Adverse effect indicated**:**:** tremors occurred in conjunction with significant brain cholinesterase inhibition. **NOEL:** (M/F) 0.25 mg/kg (based upon inhibition of brain cholinesterase activity in the 0.5 mg/kg group). **Study acceptable**. (Moore, 4/28/98)

253-271; 159979; "Reversibility Study with Carbamate Insecticides in Rats"; (L.A. Malley; E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Study No. HL-1997-00641; 11/10/97); Forty rats/sex/group were orally gavaged with 0 or 1 mg/kg of oxamyl technical (purity: 98.3%) or 0 or 3 mg/kg of methomyl technical (purity: 98.6%). Plasma, RBC, and brain cholinesterase (ChE) activities were measured for 10 animals/sex/group at 30 minutes and 2, 3 and 4 hours post-dose. Tremors were noted at 30 minutes post-dose in animals treated with both of the test materials. This sign was not evident at 2 hours after dosing. For the oxamyl treated animals, at 30 minutes after dosing, plasma, RBC and brain ChE activities were significantly inhibited (plasma: (M) 43%, (F) 50% of control; RBC: (M) 42%, (F) 39% of control; brain: (M) 55%, (F) 52%). By two hours, ChE activity had returned to control levels. Likewise, for the methomyl treated animals, at 30 minutes post-dose, plasma, RBC and brain ChE activities were significantly inhibited (plasma: (M) 73% of control; RBC: (M) 44%, (F) 59% of control; brain: (M) 54%, (F) 61% of control). By 2 hours, the ChE activities had returned to control levels. Study data indicate that significant ChE inhibition is largely reversible by 2 hours after dosing for both of the test materials. **Possible adverse effect indicated:** tremors and significant brain cholinesterase inhibition evident. **NOEL:** (oxamyl) < 1 mg/kg, (methomyl) < 3 mg/kg; **Study supplemental.** (Moore, 3/26/98)

**253-273 164573 Mikles, K. A., "Methomyl Technical (DPX-X1179-512): Subchronic oral neurotoxicity study in rats", Haskell Laboratory Project ID# DuPont HL-1998-01639, 9/25/98. Forty-two Crl:CD®BR rats/sex/group were dosed with 0, 20, 50, 150, or 1500 ppm methomyl (98.6% purity) in diet for up to 91 days. Three sets of 10/sex/dose were used in cholinesterase studies. These were sacrificed at weeks 4, 8, and 13, respectively for assays of RBC, plasma, and brain cholinesterase. The other 12/sex/dose underwent neurobehavioral testing (FOB and motor activity) at pre-test and at weeks 4, 8, and 13. Of these, six/sex/dose were perfused *in situ*. Neuropathology was performed on control and high dose central and peripheral nervous system preparations. NOEL = 150 ppm. Body weights and food consumption were markedly reduced at 1500 ppm in both sexes throughout the study. The most prominent of the clinical observations were tremors in most 1500 ppm males and females during the first 4 weeks, and occasionally thereafter. Common FOB observations included increased resistance to handling